REMARKS

Claims 1-20 are pending in the instant application. Claims 1, 2, 11, 12 and 14-20 have been rejected. Claims 3-10 and 13 have been objected to. Claims 11 and 16-20 have been canceled. Claims 1, 3 and 15 have been amended. Claim 3 has been made independent and new claims 21-32 have been added in light of the amendment making claim 3 independent; dependent claims corresponding to the subject matter of claims 2 and 4-15 have been included with respect to now independent claim 3. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. The Examiner suggests that the specification while being enabling for antisense to CD81 and their use to inhibit CD81 expression *in vitro* does not reasonably provide enablement for any

nucleic acid sequence which hybridizes to any sequence of CD81 and for *in vivo* antisense inhibition of in whole organisms; the Examiner cites published articles to support the position. Applicants respectfully traverse this rejection of the claims.

At the outset, Applicants have amended claim 1, and by dependency claims 2 and 4-20, recite CD81 nucleic acid molecules of SEQ ID NO's 3, 10 or 11, as taught in the specification as filed, in particular at pages 81-85. Therefore, the claims as amended identify particular CD81 nucleic acid molecules and meet the requirements of 112, first paragraph with respect to the claims for antisense which hybridizes with these specific CD81 nucleic acids.

With respect to the rejection of the claims and the *in vitro* to *in vivo* extrapolations of data, Applicants disagree with the Examiner's suggestion that cited references on antisense technology support the position that application of antisense *in vivo* is unpredictable.

The Examiner has pointed to articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis

to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Branch (1998) is a review article on the technology of antisense. This paper teaches the need to develop antisense molecules based on sound data and careful screening, such as presented in the instant specification. What this paper, and the others cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Flanagan et al. (1998) discusses ways to alter antisense oligonucleotides in order to enhance that permeation properties in cells. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Green et al. (2000) describes the general technology of antisense and its evolution over time. Nowhere in the reference does the author state or suggest that results of

well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Bennett et al. (1996) is an older chapter that discusses the use of antisense compounds in the treatment of cancer and inflammation. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Jen et al. (2000) also describes the general area of antisense technology as well as other ways to suppress gene expression. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The chapter by Ma et al. (2000) is another review of antisense technology. This chapter raises each of the issues that had been encountered during development of antisense but also discusses how this tool has therapeutic promise and that some have progressed to clinical trial status. Most importantly, nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

Finally, the paper by Agrawal and Kandimalia (2000) is a review of antisense therapeutics and focuses on understanding the mechanism of their activity. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

Development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. The key is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, when antisense oligonucleotides are developed using well designed studies that progress logically from activity in cells to activity in animals and humans, one of skill would expect that activity in cells would be predictive of activity *in vivo*.

However, Applicants have amended claim 15 and canceled claims 16-20 in an earnest effort to advance the prosecution and facilitate the allowance of this case. Applicants reserve the right to file a continuing application directed to this subject

matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 102

Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GebEMBL AX004402/c. The Examiner suggests that the cited sequence is a 41 mer sequence having bases 6-20 of instant SEQ ID NO: 30. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by EST AZ465883. The Examiner suggests that the cited sequence is a 19 mer sequence having bases 5-17 of instant SEQ ID NO: 49. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(a) as being anticipated by GenEMBL AX174772. The Examiner suggests that the cited sequence is a 50 mer sequence having bases 2-14 of instant SEQ ID NO: 51. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(a) as being anticipated by GenEMBL AX174772. The Examiner suggests that the cited sequence is a 18 mer sequence having bases 7-19 of instant SEQ ID NO: 52. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL AR026492. The Examiner suggests that the cited sequence is a 18 mer sequence having bases 1-13 of instant SEQ ID NO: 54. Claims 1, 2, 11, 12 and 14 have been rejected under

35 U.S.C. 102(b) as being anticipated by GenEMBL AB069260. The Examiner suggests that the cited sequence is a 18 mer sequence having bases 7-19 of instant SEQ ID NO: 60. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL AR040450. The Examiner suggests that the cited sequence is a 27 mer sequence having bases 1-14 of instant SEQ ID NO: 61. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL I76404. The Examiner suggests that the cited sequence is a 23 mer sequence having bases 7-19 of instant SEQ ID NO: 63. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by EST AZ941495. The Examiner suggests that the cited sequence is a 42 mer sequence having bases 4-16 of instant SEQ ID NO: 68. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL AX090066. The Examiner suggests that the cited sequence is a 26 mer sequence having bases 1-13 of instant SEQ ID NO: 71. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by EST AZ493934. The Examiner suggests that the cited sequence is a 39 mer sequence having bases 1-13 of instant SEQ ID NO: 75. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL I07146. The Examiner

suggests that the cited sequence is a 32 mer sequence having bases 5-17 of instant SEQ ID NO: 76. Claims 1, 2, 11, 12 and 14 have been rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL AB069260. The Examiner suggests that the cited sequence is a 18 mer sequence having bases 5-17 of instant SEQ ID NO: 88. In each case, the Examiner also suggests that the presence of identical chemical structure means that properties as claimed are present. Applicants respectfully traverse these rejections under 35 U.S.C. 102(a) and 102(b).

At the outset, Applicants have amended the claims to recite antisense compounds that are targeted to specific regions of the CD81 nucleic acid molecules of SEQ ID NO's 3, 10 and 11, or to specific sequences that do not consist of the exact sequences or portions of sequences cited by the Examiner. Support for these amendments can be found throughout the specification as filed, but in particular at pages 81-85.

Each of the sequences cited by the Examiner overlap only with up to 15 consecutive nucleobases of one sequence of the instant invention. No other exact sequences or lengths of sequences are taught or suggested by the citations listed by the Examiner, nor are regions within the sequence of CD81 nucleic acid molecules that could be targeted by antisense. Therefore, each of these

citations taken alone cannot anticipate the claims as amended, which specify antisense compounds targeted to specific regions of CD81 nucleic acid molecules, as each reference cited fails to teach each and every claim limitation (MPEP 2131). Accordingly, withdrawal of these rejections is respectfully requested.

II. Objection to the Claims

Claims 3-10 and 13 have been objected to as being dependent on rejected base claims but the Examiner suggests they would be allowable if rewritten in independent form including all of the limitations of the base claims. Applicants have amended claim 3 to be an independent claim and have added new claims 21-32 to incorporate the subject matter of claims 4-10 and 13. Accordingly, withdrawal of this objection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled.

The claims have been amended as follows:

1. (amended) A compound ~~8~~ 16 to 50 nucleobases in length targeted to a 3'-untranslated region, a coding region, a stop codon region, or a 5'-untranslated region of a nucleic acid molecule encoding CD81 of SEQ ID NO: 3, an intron 1 region, an intron 2 region, an intron 3 region, and intron:exon junction region, an exon 1 region, or an exon 8 region of a nucleic acid molecule encoding human CD81 of SEQ ID NO: 11, or a 3'-untranslated region of a nucleic acid molecule encoding human CD81 of SEQ ID NO: 10, wherein said compound specifically hybridizes with one of said regions of said nucleic acid molecule encoding CD81 and inhibits the expression of CD81.

3. (amended) ~~The~~ A compound ~~of claim 2 wherein the antisense oligonucleotide has a sequence~~ up to 50 nucleobases in length comprising at least a 16 nucleobase portion of SEQ ID NO: 14, 15, 16, 17, 20, 21, 22, 23, 24, 26, 27, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 48, 49, 51, 52, 53, 54, 55, 56,

57, 58, 59, 60, 61, 63, 64, 65, 66, 67, 68, 71, 72, 74, 75, 76, 78, 79, 80, 81, 82, 83, 86, 88 or 89 which inhibits the expression of CD81.

15. (amended) A method of inhibiting the expression of CD81 in cells or tissues comprising contacting said cells or tissues in vitro with the compound of claim 1 so that expression of CD81 is inhibited.